Serial No.: 10/045,178

Filed: January 11, 2002

Page : 2 of 25

## Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

## **Listing of Claims**:

## 1-40. (Canceled)

- 41. (Currently Amended) A method of treating a subject having a cell proliferative disorder comprising:
  - a) contacting the subject with a therapeutically effective amount of a <u>recombinant</u> replication competent oncoretrovirus, comprising:
    - a retroviral GAG protein;
    - a retroviral POL protein;
    - a retroviral envelope;
    - an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the <u>oncoretroviral genomepolynucleotide sequence</u>;
    - a cassette comprising an internal ribosome entry site (IRES) operably linked to a; a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and
    - cis-acting nucleic acid sequences involved in for reverse transcription, packaging and integration in a target cell,

## in a pharmaceutically acceptable carrier; and

b) contacting the subject with a prodrug which is activated by the expression of the suicide gene;

wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 3 of 25

42. (Original) The method of claim 41, wherein the subject is a mammal.

- 43. (Original) The method of claim 42, wherein the mammal is a human.
- 44. (Original) The method of claim 41, wherein the contacting is by in vivo administration of the retrovirus.
- 45. (Original) The method of claim 44, wherein the in vivo administration is by systemic, local, or topical administration.
- 46. (Withdrawn) The method of claim 41, wherein the contacting is by ex vivo administration of the retrovirus.
- 47. (Canceled)
- 48. (Canceled)
- 49. (Previously Presented) The method of claim 41, wherein the oncoretroviral polynucleotide sequence is selected from the group consisting of murine leukemia virus (MLV), Moloney murine leukemia virus (MoMLV), Gibbon ape leukemia virus (GALV) and Human Foamy Virus (HFV).
- 50. (Previously Presented) The method of claim 49, wherein the MLV is an amphotropic MLV
- 51. (Previously Presented) The method of claim 64, wherein the ENV protein is selected from the group consisting of murine leukemia virus (MLV) ENV protein and vesicular stomatitis virus (VSV) ENV protein.
- 52-55. (Canceled)
- 56. (Currently Amended) The method of claim 41, wherein the cell proliferative disorder is selected from the group consisting of lung cancer, colon-rectum cancer, breast cancer, prostate cancer, urinary tract cancer, uterine cancer, brain cancer, lymphoma, oral head and neck cancer, pancreatic cancer, leukemia, melanoma, stomach cancer and ovarian cancer.
- 57. (Canceled)
- 58. (Previously Presented) The method of claim 41, wherein the LTR of the retrovirus comprises a tissue-specific promoter sequence.

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 4 of 25

59. (Previously Presented) The method of claim 58, wherein the tissue-specific promoter sequence is a probasin promoter sequence or a growth regulatory gene promoter sequence.

- 60. (Canceled)
- 61. (Currently Amended) The method of claim 41, wherein the <u>oncoretrovirus is a</u>

  <u>mammalian oncoretrovirus suicide gene is a thymidine kinase or a purine nucleoside</u>

  <del>phosphorylase (PNP)</del>.
- 62. (Canceled)
- 63. (Previously Presented) The method of claim 41, wherein the retroviral envelope comprises a chimeric protein.
- 64. (Previously Presented) The method of claim 63, wherein the chimeric protein comprises an ENV protein and a targeting polypeptide.
- 65. (Previously Presented) The method of claim 64, wherein the targeting polypeptide is an antibody, a receptor, or a receptor ligand.
- 66. (Currently Amended) A method of treating a subject having a cell proliferative disorder comprising:
  - a) contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretroviral polynucleotide, comprising:
    - a polynucleotide sequence encoding a GAG protein;
    - a polynucleotide sequence encoding a POL protein;
    - a polynucleotide sequence encoding a retroviral envelope;
    - an oncoretroviral polynucleotide sequence comprising Long Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the oncoretroviral polynucleotide sequence;
    - a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous polynucleotide nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous polynucleotide nucleic acid encodes a suicide gene; and

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 5 of 25

cis acting nucleic acid sequences involved in for reverse transcription, packaging and integration in a target cell; and

- b) contacting the subject with a prodrug which is activated by the expression of the suicide gene;
- wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.
- 67. (Previously Presented) The method of claim 66, wherein the polynucleotide sequence encoding a retroviral envelope encodes a chimeric protein.
- 68. (Previously Presented) The method of claim 67, wherein the chimeric protein comprises an ENV protein and a targeting polypeptide.
- 69. (Previously Presented) The method of claim 68, wherein the targeting polypeptide is an antibody, a receptor, or a receptor ligand.
- 70. (Previously Presented) The method of claim 66, wherein the GAG, POL and retroviral envelope polynucleotide sequences are from murine leukemia virus (MLV) or Moloney murine leukemia virus (MoMLV).
- 71. (Previously Presented) The method of claim 70, wherein the MoMLV is an amphotropic MoMLV.
- 72. (Previously Presented) The method of claim 68, wherein the ENV protein is an ecotropic protein.
- 73. (Previously Presented) The method of claim 68, wherein the ENV protein is selected from the group consisting of a murine leukemia virus (MoMLV) ENV protein and vesicular stomatitis virus (VSV) ENV protein.
- 74. (Canceled)
- 75. (Currently Amended) The method of claim 6656, wherein the <u>cell proliferative disorder</u> is melanomasuicide gene encodes a thymidine kinase or a purine nucleoside phosphorylase (PNP).
- 76. (Canceled)
- 77. (Canceled)
- 78. (Previously Presented) The method of claim 66, wherein the polynucleotide sequence is contained in a viral particle.

Serial No.: 10/045,178

Filed : January 11, 2002

Page : 6 of 25

79. (Previously Presented) The method of claim 66, wherein the polynucleotide sequence is contained in a pharmaceutically acceptable carrier.

- 80. (Currently Amended) A method of treating a subject having a cell proliferative disorder comprising:
  - a) contacting the subject with a therapeutically effective amount of a recombinant replication competent murine leukemia virus (MLV), comprising:

an MLV GAG protein;

an MLV POL protein;

an MLV envelope;

an MLV polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the MLV polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and

cis-acting nucleic acid sequences necessary for reverse transcription, packaging and integration in a target cell; and

- b) contacting the subject with a prodrug which is activated by the expression of the suicide gene;
- wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.
- 81. (Currently Amended) A method of treating a subject having a cell proliferative disorder comprising:
  - a) contacting the subject with a therapeutically effective amount of a recombinant replication competent <u>oncoretrovirus</u> comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope comprising a chimeric env protein comprising a targeting ligand;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 7 of 25

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the oncoretroviral polynucleotide sequence;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and

cis-acting nucleic acid sequences involved in for reverse transcription, packaging and integration in a target cell; and

- b) contacting the subject with a prodrug which is activated by the expression of the suicide gene;
- wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.
- 82. (Currently Amended) A method of treating a subject having a cell proliferative disorder comprising:
  - a) contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretroviral polynucleotide, comprising:
    - a polynucleotide sequence encoding a GAG protein;
    - a polynucleotide sequence encoding a POL protein;
    - a polynucleotide sequence encoding a retroviral envelope, wherein said envelope comprises a chimeric env protein comprising a targeting ligand;
    - an oncoretroviral polynucleotide sequence comprising Long Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the oncoretroviral polynucleotide;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous polynucleotide nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous polynucleotide encodes a suicide gene;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 8 of 25

cis acting polynucleotide sequences involved in reverse transcription, packaging and integration in a target cell; and

b) contacting the subject with a prodrug which is activated by the expression of the suicide gene;

wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

Claims 83-86 canceled.

- 87. (Currently Amended) A method of treating glioblastoma in a subject comprising:
- a) administering a therapeutically effective amount of a <u>recombinant replication</u> competent oncoretrovirus to the subject, wherein the retrovirus comprises:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the retroviral <u>genome polynucleotide</u> sequence;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and

cis-acting nucleic acid sequences-involved in for reverse transcription, packaging and integration in a target cell; and

- b) administering a prodrug, which is activated by the expression of the suicide gene, to the subject.
- 88. (Currently Amended) The method of claim 87, wherein the regulatory nucleic acid sequence LTR comprises a tissue-specific promoter sequence.
- 89. (Currently Amended) A method of treating a glioblastoma in a subject comprising:
- a) administering a therapeutically effective amount of a recombinant retroviral polynucleotide to the subject, wherein the recombinant retroviral polynucleotide comprises: a polynucleotide sequence encoding a GAG protein;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 9 of 25

a polynucleotide sequence encoding a POL protein;

a polynucleotide sequence encoding a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the oncoretroviral polynucleotide sequence;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous polynucleotide sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous polynucleotide encodes a suicide gene; and

cis acting nucleic acid sequences involved in for reverse transcription, packaging and integration in a target cell; and

- b) administering a prodrug, which is activated by the expression of the suicide gene, to the subject.
- 90. (Currently Amended) The method of claim 89, wherein the regulatory nucleic acid sequence <u>LTR</u> comprises a tissue-specific promoter sequence.
- 91. (Currently Amended) A method of treating a glioblastoma in a subject comprising:
- a) administering a therapeutically effective amount of a recombinant replication competent murine leukemia virus (MLV) to the subject, wherein the recombinant replication competent MLV comprises:

an MLV GAG protein;

an MLV POL protein;

an MLV envelope;

an MLV polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the MLV polynucleotide sequence;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and

cis-acting nucleic acid sequences <del>necessary</del> for reverse transcription, packaging and integration in a target cell; and

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 10 of 25

b) administering a prodrug, which is activated by the expression of the suicide gene, to the subject.

- 92. (Currently Amended) The method of claim 91, wherein the regulatory nucleic acid sequence LTR comprises a tissue-specific promoter sequence.
- 93. (Currently Amended) A method of treating a glioblastoma in a subject comprising:
- a) administering a therapeutically effective amount of a recombinant replication competent <u>oncoretrovirus</u> to the subject, wherein the recombinant replication competent <u>oncoretrovirus</u> comprises:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope comprising a chimeric env protein comprising a targeting ligand;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the oncoretroviral polynucleotide sequence;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid encodes a suicide gene; and

cis-acting nucleic acid sequences involved in for reverse transcription, packaging and integration in a target cell; and

- b) administering a prodrug, which is activated by the expression of the suicide gene, to the subject.
- 94. (Currently Amended) The method of claim 93, wherein the regulatory nucleic acid sequence <u>LTR</u> comprises a tissue-specific promoter sequence.
- 95. (Currently Amended) A method of treating a glioblastoma in a subject comprising:
- a) administering a therapeutically effective amount of a recombinant <u>oncoretroviral</u> polynucleotide to the subject, wherein the recombinant <u>oncoretroviral</u> polynucleotide comprises:
  - a polynucleotide sequence encoding a GAG protein;
  - a polynucleotide sequence encoding a POL protein;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 11 of 25

a polynucleotide sequence encoding a retroviral envelope, wherein said envelope comprises a chimeric env protein comprising a targeting ligand;

an oncoretroviral polynucleotide sequence comprising Long Terminal Repeat (LTR) sequences at the <u>5' or 3' or 5'</u> and 3' ends of the oncoretroviral polynucleotide <u>sequence</u>;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous polynucleotide sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope operably linked to a regulatory nucleic acid sequence, wherein the heterologous polynucleotide encodes a suicide gene;

cis acting polynucleotide sequences involved in for reverse transcription, packaging and integration in a target cell; and

- b) administering a prodrug, which is activated by the expression of the suicide gene, to the subject.
- 96. (Currently Amended) The method of claim 95, wherein the regulatory nucleic acid sequence LTR comprises a tissue-specific promoter sequence.
- 97. (New) A method of treating a subject having a cell proliferative disorder comprising: contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretrovirus comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell,

wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 12 of 25

98. (New) The method of claim 97, wherein the cell proliferative disorder is selected from the group consisting of lung cancer, colon-rectum cancer, breast cancer, prostate cancer, urinary tract cancer, uterine cancer, brain cancer, lymphoma, head and neck cancer, pancreatic cancer, melanoma, stomach cancer and ovarian cancer.

- 99. (New) The method of claim 97, wherein the oncoretrovirus is a mammalian oncoretrovirus.
- 100. (New) A method of treating a subject having a cell proliferative disorder comprising: contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretroviral polynucleotide, comprising:
  - a polynucleotide sequence encoding a retroviral GAG protein;
  - a polynucleotide sequence encoding a retroviral POL protein;
  - a polynucleotide sequence encoding a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell, wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

- 101. (New) The method of claim 100, wherein cell proliferative disorder is melanoma.
- 102. (New) A method of treating a subject having a cell proliferative disorder comprising: contacting the subject with a therapeutically effective amount of a recombinant replication competent murine leukemia virus (MLV), comprising:

an MLV GAG protein;

an MLV POL protein;

an MLV envelope;

an MLV polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the MLV polynucleotide sequence;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 13 of 25

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell, wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

- 103. (New) A method of treating a subject having a cell proliferative disorder comprising: contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretrovirus comprising:
  - a retroviral GAG protein;
  - a retroviral POL protein;
  - a retroviral envelope comprising a chimeric env protein comprising a targeting ligand; an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and
  - cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell, wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.
- 104. (New) A method of treating a subject having a cell proliferative disorder comprising: contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretroviral polynucleotide, comprising:
  - a polynucleotide sequence encoding a retroviral GAG protein;
  - a polynucleotide sequence encoding a retroviral POL protein;
  - a polynucleotide sequence encoding a retroviral envelope, wherein said envelope comprises a chimeric env protein comprising a targeting ligand;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 14 of 25

an oncoretroviral polynucleotide sequence comprising Long Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell, wherein the cell proliferative disorder is a neoplastic disorder or associated with an overgrowth of connective tissue.

105. (New) A method of treating glioblastoma in a subject comprising:
administering a therapeutically effective amount of a recombinant replication competent oncoretrovirus to the subject, wherein the oncoretrovirus comprises:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell.

- 106. (New) The method of claim 105, wherein the LTR comprises a tissue specific promoter sequence.
- 107. (New) A method of treating glioblastoma in a subject comprising:

  administering a therapeutically effective amount of a recombinant oncoretroviral

  polynucleotide to the subject, wherein the recombinant oncoretroviral polynucleotide

  comprises:
  - a polynucleotide sequence encoding a GAG protein;

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 15 of 25

a polynucleotide sequence encoding a POL protein;

a polynucleotide sequence encoding a retroviral envelope;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell.

- 108. (New) The method of claim 107, wherein the LTR comprises a tissue specific promoter sequence.
- 109. (New) A method of treating glioblastoma in a subject comprising:

  administering a therapeutically effective amount of a recombinant replication competent murine leukemia virus (MLV) to the subject, wherein the recombinant replication competent MLV comprises:

an MLV GAG protein;

an MLV POL protein;

an MLV envelope;

an MLV polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the MLV polynucleotide sequence;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell.

- 110. (New) The method of claim 109, wherein the LTR comprises a tissue specific promoter sequence.
- 111. (New) A method of treating glioblastoma in a subject comprising:

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 16 of 25

administering a therapeutically effective amount of a recombinant replication competent oncoretrovirus to the subject, wherein the recombinant replication competent oncoretrovirus comprises:

a retroviral GAG protein;

a retroviral POL protein;

an retroviral envelope comprising a chimeric env protein comprising a targeting ligand; an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the MLV polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell.

- 112. (New) The method of claim 111, wherein the LTR comprises a tissue specific promoter sequence.
- 113. (New) A method of treating glioblastoma in a subject comprising:
  administering a therapeutically effective amount of a recombinant oncoretroviral
  polynucleotide to the subject, wherein the recombinant oncoretroviral polynucleotide
  comprises:
  - a polynucleotide sequence encoding a GAG protein;
  - a polynucleotide sequence encoding a POL protein;
  - a polynucleotide sequence encoding a retroviral envelope, wherein said envelope comprises a chimeric env protein comprising a targeting ligand;

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 17 of 25

cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell.

- 114. (New) The method of claim 113, wherein the LTR comprises a tissue specific promoter sequence.
- 115. (New) The method of claim 99, wherein the mammalian oncoretrovirus is selected from the group consisting of murine leukemia virus (MLV), Moloney murine leukemia virus (MoMLV), and Gibbon ape leukemia virus (GALV).
- 116. (New) The method of claim 97, wherein the cytokine is selected from the group consisting of interleukins 1 through 12, interferon, tumor necrosis factor (TNF), and granulocyte-macrophage-colony stimulating factor (GM-CSF).
- 117. (New) The method of claim 116, wherein the cytokine is interferon.
- 118. (New) The method of claim 117, wherein the interferon is gamma interferon.
- 119. (New) A method of treating a subject having a cell proliferative disorder comprising: contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretrovirus comprising:
  - a retroviral GAG protein;
  - a retroviral POL protein;
  - a retroviral or non-retroviral envelope;
  - an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a cytokine; and
  - cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a target cell.
- 120. (New) The method of claim 119, wherein the non-retroviral envelope is derived from VSV, CMV or influenza virus.
- 121. (New) A method of treating a subject having a cell proliferative disorder comprising:

Serial No.: 10/045,178 Filed: January 11, 2002

Page : 18 of 25

contacting the subject with a therapeutically effective amount of a recombinant replication competent oncoretrovirus comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

target cell.

an oncoretroviral polynucleotide sequence comprising Long-Terminal Repeat (LTR) sequences at the 5' or 3' or 5' and 3' ends of the oncoretroviral polynucleotide sequence; a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence, wherein the cassette is positioned 5' to the 3' LTR and 3' to the sequence encoding the retroviral envelope, wherein the heterologous nucleic acid encodes a suicide gene; and cis-acting nucleic acid sequences for reverse transcription, packaging and integration in a